On Nonrandomized, Randomized, and Fuzzy *p*-Values in Multiple Hypothesis Testing: A Unified Approach

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Example $X \sim Bin(11, p)$

1. Model: $X \sim Bin(11, p)$
2. Hypotheses: $H_0 : p = 1/2$ vs. $H_1 : p > 1/2$
3. Data: $X = 8$
4. p-value:
    - Conventional p-value = $\Pr_X(X \geq 8) = 0.11$
    - Mid p-value = $\Pr_X(X > 8) + 1/2 \Pr_X(X = 8) = 0.072$ [1]
5. Conclusion: Fail to reject H_0 at $\alpha = 0.05$.

[1] Lancaster (1961)

Reconciliation

Client: "But the mid-p-value is almost 0.05!!!"

Statistician: "Well the type 1 error rate for mid-p-value-based decision $\approx$ 0.05"

Proposed Statement: "The mid-p-value is 0.072 and is conservative for a level $\alpha = 0.05$ decision rule"[2]

[2]Note: Actual type 1 error rate = $\Pr_X^0(X \geq 9) = 0.033$

Goals

Main Points:

1. Communicate the behavior (liberal/conservative/etc.) of decision rule - especially in borderline cases
    - Behavior understood via test function $\phi(x)$
2. How can we compute $\phi(x)$ in complicated settings, ex. multiple hypothesis testing?

Test Function

- Let X have countable support and consider H_0 vs. H_1

- A **Size α test function** $\phi(x;\alpha)$
  - $\phi(x;\alpha) \in [0,1]$
  - $E_X[\phi(X;\alpha)] = \alpha$ under H_0

-Example

$$\phi^*(x;\alpha) = \begin{cases} 1 & x > k(\alpha) \\ \gamma(\alpha) & x = k(\alpha) \\ 0 & x < k(\alpha) \end{cases}$$

Decision function and p-value

- If $\phi(x;\alpha) \in (0,1)$ make decision using $u \in (0,1]$
  - Decision function: $\delta(x,u;\alpha) = I(u \leq \phi(x;\alpha)) \in \{0,1\}$
  - p-value: $p(x,u) = \inf\{\alpha : \delta(x,u;\alpha) = 1\}$[3]
- Example: $X \sim Bin(11,p)$ with

$$\phi^*(x;0.05) = \begin{cases} 1 & x > 8 \\ 0.21 & x = 8 \\ 0 & x < 8 \end{cases}$$

  - $\delta^*(8,u;0.05) = I(u \leq 0.21)$
  - $p^*(8,u) = \Pr_X(X > 8) + u \Pr_X(X = 8) = 0.033 + u0.081$

[3] Habiger and Peña(2011), Peña, Habiger, Wu (2012)

How to produce u?

- $\delta(x, u; \alpha)$ and $p(x, u)$ are
  - **nonrandomized** if u **chosen**
    - Mid-p-value $p(x, 1/2)$
    - Conventional p-value $p(x, 1)$
  - **randomized** if u **generated**

- $p(x, U)$ is an **abstract randomized** (fuzzy) p-value[4] if $U \sim Un(0, 1)$
  - Example:
    $p^*(8, U) = 0.033 + U0.081 \sim Un(0.033, 0.114)$

[4] Geyer and Meeden (2005)

Proposed Method

Step 1 **Compute $\phi(x;\alpha)$. Reject or fail to reject H_0 if possible and stop. Else report $p(x,U)$ and $\phi(x;\alpha)$ and go to Step 2a or Step 2b.**

Step 2a **Generate u**, compute $\delta(x,u;\alpha)$ and $p(x,u)$

Step 2b **Specify u**, compute $\delta(x,u;\alpha)$ and $p(x,u)$

- *Usual Approach: Go directly to Step 2a or Step 2b*

- Viewpoint[5]: Goal to "estimate" $\phi(x;\alpha) \in [0,1]$ with $\delta(x,u;\alpha) \in \{0,1\}$

[5] Blyth and Staudte (1995)

Step 1 vs. 2a

Q: What if we only report $\delta(x, u; \alpha)$ but not $\phi(x; \alpha)$ in Step 2a?

Mathematical Answer:

Theorem

Let U be uniformly distributed over $[0, 1]$ and independent of X, then the following claims are true:

C1: $E_U(\delta(x, U; \alpha)) = \phi(x; \alpha)$ *and hence* $E_{(X,U)}[\delta(X, U; \alpha)] = E_X[\phi(X; \alpha)]$ *(unbiased),*

C2: $Var(\delta(X, U; \alpha)) \geq Var(\phi(X; \alpha))$.

Intuitive Answer: Information loss

- Did $\delta(x, u; \alpha)$ depend on u?

Step 1 vs. 2b

Q: What if we only report $\delta(x, u; \alpha)$ but not $\phi(x; \alpha)$ in Step 2a?

Mathematical Answer:

Theorem

For any fixed or specified value of u,

C3: $E_X[\delta^*(X, u; \alpha)] \neq E_X[\phi^*(X; \alpha)]$ *(biased) for every* $\gamma(\alpha) \in (0, 1)$. *In particular,* $E_X[\delta^*(X, u; \alpha)] > (<) E_X[\phi^*(X; \alpha)]$ *for* $\gamma(\alpha) < (\geq) u$, *ex.* $u > \gamma \Rightarrow$ *decision conservative (size* $< \alpha$*)*

Intuitive Answer: Information loss

- Did $\delta(x, u; \alpha)$ depend on u?
- Is $\delta(x, u; \alpha)$ conservative or liberal?

Example: $u = 1/2 > 0.21 = \phi^*(8; 0.05) \Rightarrow$ size $< \alpha$.

Multiple decision function

Brief overview:

- Goal: Test H_{0m}, $m = 1, 2, ..., M$ null hypotheses with data $\mathbf{x} = (x_1, x_2, ..., x_M)$ and $\mathbf{u} = (u_1, u_2, ..., u_M)$
- p-values $\mathbf{p} = \mathbf{p}(\mathbf{x}, \mathbf{u}) = [p_1(x_1, u_1), p_2(x_2, u_2), ..., p_M(x_M, u_M)]$
- Multiple Testing procedure is a multiple decision function (MDF)

$$\boldsymbol{\delta}(\mathbf{x}, \mathbf{u}; \alpha) = [\delta_1(\mathbf{x}, \mathbf{u}; \alpha), \delta_2(\mathbf{x}, \mathbf{u}; \alpha), ..., \delta_M(\mathbf{x}, \mathbf{u}; \alpha)] \in \{0, 1\}^M$$

where $\delta_m(\mathbf{x}, \mathbf{u}; \alpha) = \delta_m(\mathbf{p}(\mathbf{x}, \mathbf{u}); \alpha)$

Example: Benjamini and Hochberg (1995)

1. $k(\mathbf{p}) = \max\left\{i : p_{(i)} \leq \alpha \frac{i}{M}\right\}$
2. $\delta_m^{BH}(\mathbf{x}, \mathbf{u}; \alpha) = I\left(p_m(x_m, u_m) \leq \alpha \frac{k(\mathbf{p})}{M}\right)$

Adjusted *p*-values

Adjusted *p*-value for MTP:

$$q_m(\mathbf{x}, \mathbf{u}) = \inf\{\alpha : \delta_m(\mathbf{x}, \mathbf{u}; \alpha) = 1\}$$

- **Adjusted nonrandomized** *p*-value $q_m(\mathbf{x}, \mathbf{u})$: $\mathbf{u}$ is chosen
- **Adjusted randomized** *p*-value $q_m(\mathbf{x}, \mathbf{u})$: $\mathbf{u}$ generated
- **Adjusted abstract randomized** (fuzzy) *p*-value $q_m(\mathbf{x}, \mathbf{U})$
  - We can easily sample from $q_m(\mathbf{x}, \mathbf{U})$ via $q_m(\mathbf{x}, \mathbf{u}^1), q_m(\mathbf{x}, \mathbf{u}^2), \ldots$ and construct a histogram

Remark: $q_m(\mathbf{x}, \mathbf{u})$ can often be computed with software

Multiple Test Function

Idea: Recall $\phi(x;\alpha) = E_U[\delta(x, U;\alpha)]$.

Definition

Define multiple test function

$$\boldsymbol{\phi}(\mathbf{x};\alpha) = [\phi_1(\mathbf{x};\alpha), \phi_2(\mathbf{x};\alpha), ..., \phi_M(\mathbf{x};\alpha)] \in [0,1]^M$$

where

$$\phi_m(\mathbf{x};\alpha) = E_{\mathbf{U}}[\delta_m(\mathbf{x},\mathbf{U};\alpha)] = \int_0^1\int_0^1 ... \int_0^1 \delta_m(\mathbf{x},\mathbf{u};\alpha)du_1du_2...du_M$$

for $m = 1, 2, ..., M$.

Remark: each $\phi_m(\mathbf{x};\alpha)$ can be easily computed numerically.

Microarray Example

Table: A portion of the microarray data in Timmons et. al (2007).

gene	brown fat cell				white fat cell			
m	$x_{m,1}$	$x_{m,2}$	...	$x_{m,10}$	$y_{m,1}$	$y_{m,2}$	...	$y_{m,14}$
1	1.22	1.66	...	1.41	5.64	1.79	...	11.50
2	3.57	19.22	...	5.23	5.17	29.49	...	7.58
.	.	.	...	.	.	.	...	.
.	.	.	...	.	.	.	...	.
M=12488	2.52	10.91	...	22.67	10.70	7.35	...	21.95

1. Compute shifted Wilcoxon rank sum stat: $w_m = \left| w_m^* - \frac{14x10}{2} \right|$
2. Compute $p_m^*(w_m, u_m) = \Pr_W(W_m > w_m) + u_m \Pr_W(W_m = w_m)$
3. Apply MTP: Storey (2002, 2004) adaptive FDR procedure using $q.value()$ with $\alpha = 0.05$.

Step 2a

- What if skip step 1, generate ***u***, and apply MTP

Step 1	$\phi_m(\mathbf{x}; 0.05)$	0	1	????
	Count	????	????	????
			↙	
Step 2a	Count	9315	3173	

Step 1 + 2a

- What information did Step 1 provide?

Step 1	$\phi_m(\mathbf{x}; 0.05)$	0	1	**0.94**
	Count	9302	3033	**153**
Step 2a	Count	9315	3173	↙

Step 1 tells us . . .

- 153 decisions made randomly!
- 140 genes “discovered” randomly!

Step 2b

- What if we **skip Step 1**, choose $u = 1/2$, and apply MTP

Step 1	$\phi_m(\mathbf{x}; 0.05)$	0	1	????
	Count	????	????	????
			↙	
Step 2b	Count	9302	3186	

Step 1 + 2b

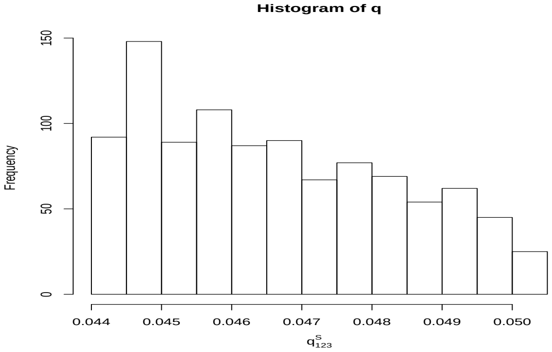
- What information did Step 1 provide?

Step 1	$\phi_m(\mathbf{x}; 0.05)$	0	1	**0.94**
	Count	9302	3033	**153**
				↙
Step 2b	Count	9302	3186	

Step 1 tells us . . .

- 153 genes "discovered" because $u = 1/2 < 0.94$
- **Procedure Liberal**

Adjust Fuzzy *p*-value



- $0.044 \leq q_m(\mathbf{x}, \mathbf{U}) \leq 0.051$
- Observe Theorem: $\Pr_{\mathbf{U}}(q_m(\mathbf{x}, \mathbf{U}) \leq \alpha) = \phi_m(\mathbf{x}) = 0.94$

Main Point

Main Point

1. Like it or not must specify or generate u to make some decisions
2. We should tell our clients when decisions were made with u and report liberal/conservative/etc behavior
   - $\phi(x)$ and $p(x, U)$ useful here

In Practice

1. Not simpler but . . . "as simple as possible?"

Loose ends

- When supports of test statistics equal
  - ~~$u_1 = u_2 = ...u_M = u = 1/2$~~
  - $u_1 = \frac{1}{M+1}, u_2 = \frac{2}{M+1}, \ldots, u_M = \frac{M}{M+1}$
- When supports of test statistics not equal - Tarone (1990)

$$\begin{array}{c}\text{Step 0: Automatically accept some } H_{0m}\text{s} \\ \Downarrow \\ \text{Step 1: Applied to remaining } H_{0m}\text{s as usual} \\ \Downarrow \\ \text{Step 2: Applied to remaining } H_{0m}\text{s as usual}\end{array}$$

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